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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,121	06/01/2007	Jakob Felding	20517/0205421-US0	4503

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DARBY & DARBY P.C.
P.O. BOX 770
Church Street Station
New York, NY 10008-0770

EXAMINER	
ANDERSON, JAMES D	
ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/599,121	FELDING ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-7,21,23-29 and 31-38* is/are pending in the application.

4a) Of the above claim(s) *26,27 and 31-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-7,21,23-25,28,29 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 12/29/2009, are acknowledged and entered. Claims 26, 27, and 31-37 remain withdrawn from consideration and being drawn to non-elected subject matter. Claims 1, 4-7, 21, 23-25, 28, 29, and 38 are presently under examination and are the subject of this Office Action.

Response to Arguments

Applicants' arguments, filed 12/29/2009, have been fully considered and are persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

The Examiner previously rejected claims 1, 4-8, 21, 23-25, 28, and 38 under 35 U.S.C. 103(a) as being unpatentable over Halperin *et al.* (US 2007/0099976 A1). Applicants have persuasively argued that one skilled in the art would not have identified Halperin's compound 1259 as a starting point to arrive at the compounds called for in the instant application. Briefly, Applicants' elected compound and compounds of formula (I) as recited in the instant claims require that X^1 and X_2 be hydroxy or acetoxy. Compound 1259 of Halperin, which requires modification to arrive at compounds encompassed by Applicants' claimed compound of formula (I), is the only compound disclosed in Table 6 of Halperin to have both a negative result in the calcium depletion assay and to fail to reduce cell growth of A549 lung cancer cells at the test concentrations. As such, Applicants' argument that one skilled in the art would conclude that compound 1259 is one of the least promising compounds within the series of compounds disclosed in Halperin is persuasive.

Upon further consideration of the scope of Applicants' claims, the Examiner is herein applying a new ground of rejection under 35 U.S.C. 112, 1st Paragraph (Scope of

Enablement). In light of the new ground of rejection, which was not necessitated by Applicants' claim amendments, this Office Action is **Non-Final**.

Claim Rejections - 35 USC § 112 (1st Paragraph)

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-7, 21, 23-25, 28, 29, and 38 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating breast cancer or prostate comprising administering compound 41 (elected compound), does not reasonably provide enablement for treating other cancers comprising administering compound 41. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a Scope of Enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill of those in the art

The invention relates to the treatment of resistant tumors, metastasizing tumors or tumors sensitive to angiogenesis inhibitors.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases

involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).As illustrative of the state of the art, the examiner cites Sausville *et al.* (Cancer Research, 2006, vol. 66, pages 3351-3354) and Johnson *et al.* (British J. of Cancer, 2001, 84(10):1424-1431).

Sausville *et al.*, cited for evidentiary purposes, teaches that traditionally explored tumor model systems are insufficient to predict how actual human beings will respond to treatment in the clinic (page 3351, left column). Even when drugs with evidence of anticancer activity in preclinical *in vivo* models are given their maximum tolerated dose in humans, they frequently fail to produce useful activity in humans (*id.*). Also, with regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

Uddin *et al.* (Bioorg. Med. Chem. Lett., 2007, vol. 17, pages 2854-2857) is provided as evidence that the R group substituents have a significant impact on the ability of compounds of the invention, *e.g.*, analogs of the elected Compound 41, to inhibit cancer cell growth and proliferation. In this regard, whereas analogs of Compound 41 wherein R is halogen or a small alkyl group in the 5 or 6 position (R2 and R3 in

compounds of Formula (I) recited in the instant claims) were potent inhibitors of MDA-468 breast cancer cell proliferation (IC_{50}s less than 0.2 μM), analogs of Compound 41 wherein R is 5-Ph, 5-(2-thienyl), 5-(4-pyridyl), or COOH were "not active" (IC_{50} > 3 μM) (Table 2). Likewise, analogs of Compound 41 wherein R1 in the compounds of Formula (I) recited in the instant claims is *i*-propyl, *t*-butyl, phenyl, 2-thienyl, 4-pyridyl, COOH, and CONMe2 were "not active" (IC_{50} > 3 μM) in inhibiting growth/proliferation of MDA-468 breast cancer cells (Table 3). Table 4 demonstrates that halogen and methyl-substituted analogs of Compound 41 were all active as was the cyclopentyl substituent. However, changing the cyclopentyl to a cyclohexyl resulted in a compound that was "not active".

These articles plainly demonstrate that the art of treating cancer, particularly in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers. This is especially true in the case of the instantly claimed compounds of Formula (I), which Uddin *et al*. demonstrate to be sensitive to variations in the substituents thereon, *i.e*., only halogen or small alkyl group substituents are active – larger groups are "not active".

2. The breadth of the claims

The claims vary in breadth; some (such as claim 1) vary broadly, reciting the treatment of cancer with a broad genus of compounds. Others, such as claim 28, are narrower, reciting specific species of the claimed genus of compounds. All, however, are extremely broad insofar as they disclose the general treatment of cancer with the same compounds.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides an *in vitro* working example wherein MDA-468 and MDA-231 human breast cancer cells were used to evaluate the anti-cancer potential of the disclosed compounds (page 50, line 27 to page 51, line 9; Figure 1). The elected

compound, compound 41, had an IC_{50} of 0.002 μM against MDA-468 cells and an IC_{50} of 13 μM against MDA-231 breast cancer cells.[2] Further, whereas most tested compounds had IC_{50} of less than 1 μM against MDA-468 breast cancer cells, all tested compounds were much less effective against MDA-231 breast cancer cells (all IC_{50}s were greater than 3 μM). Applicants state at page 52, line 3 that, "[T]he inhibitory effect of Compound 3 is therefore **very specific** for MDA-MB-468" (emphasis added).

The specification provides an *in vivo* working example wherein Compound 3 was demonstrated to inhibit growth of PRXF PC3M prostate cancer tumors (page 53, line 30 to page 54, line 10; Figure 6).

Example 6 (page 54, line 14 to page 58, line 3) provides an *in vitro* working example wherein a panel of breast cancer cell lines, prostate cancer cell lines, and a colon cancer cell line were used to evaluate the anti-cancer potential of compounds 3 and 21. Compounds 3 and 21 were **not** effective in inhibiting the growth of MDA-MB-435S, MDA-MB-231, or ZR75-1 breast cancer cells or DU-145 and PC-3/M prostate cancer cells. The only data for the Colo205 colon cancer cell line is for Compound 3 in 10% FBS.

The specification provides *in vivo* working examples wherein Compound 3 and Compound 41 were demonstrated to inhibit growth of MDA-MB-468 breast cancer tumors (page 58, lines 5-23; Figures 15 and 16) and Compound 41 was demonstrated to inhibit growth of MCF-7 breast cancer tumors (page 58, line 25 to page 59, line 12; Figure 17).

Applicants describe formulations at pages 30-32. Doses required to practice their invention are described at pages 32-33. A 2,500-fold range of doses is recommended (*e.g.*, 0.1 to 250 mg/kg). Since only three closely related compounds as instantly claimed has ever been used to treat any human cancer, how is the skilled physician to know what dose to use for each of these pathologically different cancers and structurally diverse compounds?

[2] MDA-MB-468 breast cancer cells are estrogen-receptor (ER)-negative breast cancer cells.

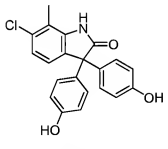
4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly elected compound (Compound 41) could be predictably used as a treatment for all cancers as inferred in the claims and contemplated by the specification.

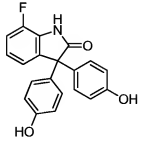
Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because Compounds 3, 21, and 41 inhibit breast and prostate cancer cell growth *in vitro* and *in vivo* then they must therefore, *a priori*, be useful in the treatment of all cancers. However, the state of the art with regard to oncology is such that different cancers require different chemotherapeutic agents for their treatment (*i.e.*, there is no "magic bullet" that is capable of treating all cancer types).

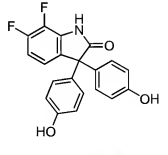
Applicants tested three closely related compounds. Note that the tested compounds differ only in the R1 and R2 substituents as defined in the compound of general formula (I) (claim 1).



Compound 3



Compound 21



Compound 41

Whereas the tested compounds comprise halogens and/or a small alkyl group in the R1 and/or R2 positions, the claims encompass compounds wherein R1, R2, R3, and R4 substituents are selected from hydrogen, optionally substituted Cl-6-alkyl, optionally substituted C2-6-alkenyl, hydroxy, optionally substituted Cl-6-alkoxy, optionally

substituted C2-6-alkenyloxy, carboxy, optionally substituted C1-6-alkoxycarbonyl, optionally substituted C1-6-alkylcarbonyl, optionally substituted Cl-6-alkylcarbonyloxy, formyl, amino, mono- and di(Cl-6-alkyl)amino, carbamoyl, mono- and di(Cl-6-alkyl)aminocarbonyl, C1-6- alkylcarbonylamino, Cl-6-alkylsulphonylamino, cyano, carbamido, mono- and di(Cl-6- alkyl)aminocarbonylamino, Cl-6-alkanoyloxy, Cl-6-alkylsulphonyl, Cl-6-alkylsulphinyl, aminosulfonyl, mono- and di(C1-6-alkyl)aminosulfonyl, nitro, optionally substituted Cl-6-alkylthio, aryl, aryloxy, arylcarbonyl, arylamino, heterocyclyl, heterocyclyloxy, heterocyclylamino, heterocyctylcarbonyl, heteroaryl, heteroaryloxy, heteroarylamino, heteroarylcarbonyl, and halogen, where any C1-6-alkyl as an amino substituent is optionally substituted with hydroxy, C1-6-alkoxy, amino, mono- and di(C1-6-alkyl)amino, carboxy, C1-6-alkylcarbonylamino, C1-6-alkylaminocarbonyl, or halogen(s), and wherein any aryl, heterocyclyl and heteroaryl may be optionally substituted; or R1 and R2 together with the carbon atoms to which they are attached form a ring.

In view of the fact that a) the tested compounds demonstrated different activities in different cancer cell lines and b) the tested compounds are closely related with minor differences in their chemical substituents and are not representative of the broad scope of the claimed compounds, it is not predictable that said compounds will be effective in the general treatment of all cancers. As discussed above, Uddin *et al.* is provided as evidence that the R group substituents have a significant impact on the ability of compounds of the invention, *e.g.*, analogs of the elected Compound 41, to inhibit cancer cell growth and proliferation. In this regard, whereas analogs of Compound 41 wherein R is halogen or a small alkyl group in the 5 or 6 position (R2 and R3 in compounds of Formula (I) recited in the instant claims) were potent inhibitors of MDA-468 breast cancer cell proliferation (IC_{50}s less than 0.2 M), analogs of Compound 41 wherein R is 5-Ph, 5-(2-thienyl), 5-(4-pyridyl), or COOH were "not active" ($IC_{50} > 3$ M) (Table 2). Likewise, analogs of Compound 41 wherein R1 in the compounds of Formula (I) recited in the instant claims is *i*-propyl, *t*-butyl, phenyl, 2-thienyl, 4-pyridyl, COOH, and CONMe2 were "not active" ($IC_{50} > 3$ M) in inhibiting growth/proliferation of MDA-468 breast cancer cells (Table 3). Table 4 demonstrates that halogen and methyl-substituted analogs of Compound 41

were all active as was the cyclopentyl substituent. However, changing the cyclopentyl to a cyclohexyl resulted in a compound that was "not active".

It is evident that a very small percentage of the claimed compounds were actually synthesized and tested for anticancer activity by Applicants and all of the synthesized compounds were related in structure. Further, the compounds tested for anticancer activity were only tested against three cancer types *in vitro* and two cancer types *in vivo*. One skilled in the art of oncology would not expect that a compound that inhibits breast and prostate cancer tumor growth *in vivo* would necessarily be effective to treat, for example, pancreatic cancer or leukemia.

Determining if any particular claimed compound would treat any particular cancerous disease state would require synthesis of the compound, formulation into a suitable dosage form, and subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction and working examples provided by Applicants. As noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Allowable Subject Matter

While examination of the instant application has been limited to the elected species (Compound 41), the Examiner notes that Applicants have enabled one skilled in the art to treat prostate or breast cancer comprising administering Compound 41, or more broadly, a compound of general formula (I) wherein R1, R2, R3, and R4 are independently selected from hydrogen, optionally substituted $C_{1\text{-}6}$-alkyl, or halogen; and X1 and X2 are independently selected from hydroxy and acetoxy. Claims limited to such a method of treatment would be allowable.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Primary Examiner, Art Unit 1614

April 8, 2010